Pharmacodynamics

Introduction

Pharmacodynamics means "biochemistry for pharmacology." We're talking about **enzymes**. And we have an entire lesson series dedicated to the topic in Biochemistry, DNA to Protein (#16: *Amino Acids* through #18: *Inhibitors and Activators*). You do NOT need to have done those lessons to understand this one. But we'll go quickly, using concepts and equations without fully explaining them. We pack three lessons' worth of the biochemistry you need for pharmacology into just this one lesson. We do this because even if you have done Biochemistry already, we'll be throwing around activators and inhibitors as we discuss drugs of the autonomic nervous system—this is your crash-course refresher. If you find yourself struggling with this lesson, take a trip back to Biochemistry and do those lessons in detail.

Vocabulary

An **agonist** is anything that **binds to an enzyme** and **activates it**. It's easiest if we just say that the **binding site** of an enzyme is where the agonist goes to make the enzyme work. A compound that binds to the binding site and makes the enzyme do what it does is an agonist. Agonists have an **affinity** (how much the enzyme likes to bind to the drug), an **efficacy** (the maximum rate of activity), and a **potency** (more on this later).

An **antagonist** is anything that prevents the activity of the enzyme. Antagonists have an **efficacy of 0**. Antagonists do NOT cause the function of an enzyme to go negative. When they bind to an enzyme, and they can bind anywhere—active binding site or somewhere else—they make the enzyme NOT DO what it's supposed to do when activated. This distinction is crucial. In the presence of an inactive enzyme, an antagonist doesn't do anything. In the presence of an inactive enzyme, an agonist activates it. Then, if the antagonists is added to the agonist-enzyme combo, the antagonist undoes the activity.

The vagueness, the biochemical inaccuracy, is intentional. I want you at a higher order of understanding. Agonists make the enzyme go; they bind to a particular site. Antagonists make the enzyme not go. They can bind to the agonist's particular site or another site, but they still make the enzyme not go. "Go" means "efficacy" means "has a dose-response curve." Agonists have one. Antagonists don't.

Types of Antagonism

1. **Physiologic antagonism** is how our bodies work. There are competing systems. The effects of activating one system can oppose the activation of another. Most physiologic systems function by activation, by agonism. We manufacture drugs to manipulate those systems, so our drugs can be antagonists or agonists. In normal physiology, it's usually the net effect, which of the two systems has more activity, that determines the physiologic effect. The **autonomic nervous system**, for example, demonstrates physiologic antagonism. The **sympathetic fight or flight** mechanism dilates pupils, increases heart rate, heightens awareness, tightens sphincters, and gets ready to run away or fight; it's activated by adrenergics (#10: *Adrenergics (SNS)*). The **parasympathetic rest and digest** mechanism does the opposite—constricts pupils, lowers heart rate, lessens awareness, relaxes sphincters, and gets you relaxed and easy. It's activated by the cholinergic system (#9: *Cholinergics (PNS)*). They oppose each other in that the activity of one is the opposite of the other, but they don't directly inhibit the receptors of the other. Norepinephrine (an adrenergic) activates adrenergic receptors but does NOT BLOCK cholinergic receptors. Acetylcholine (a cholinergic) activates cholinergic receptors but does NOT BLOCK adrenergic. The **physiologic effect is opposition** of downstream targets (cytoplasmic proteins, ion channels, or gene transcription), but there's no change at the level of the receptors themselves.

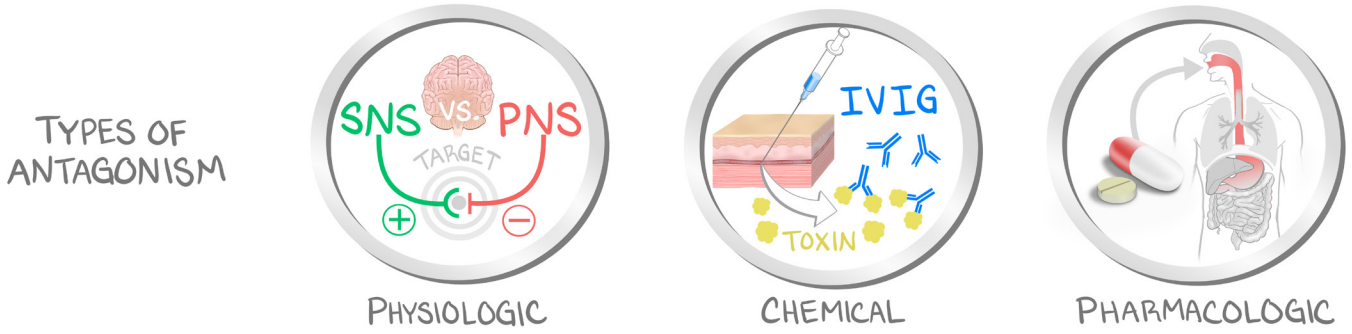

Figure 6.1: Types of Antagonism
Physiologic antagonism as activity of two competing systems; chemical antagonism that binds the drug, preventing it from reaching its receptor; and pharmacologic, which is artificial exogenous influencing of the endogenous systems.

1. **Chemical antagonism** doesn't involve receptors at all. Chemical antagonism is a means of sequestering a drug from the receptors, from the enzyme, altogether. The drug has to be administered, absorbed, and distributed before it can have effect. If we intervene at any step (intestinal binder to block absorption, antidote administered to the blood), the chemical antagonism ensures that the **drug will never see its intended receptor**. It doesn't alter enzyme kinetics; it simply prevents the drug from getting to those enzymes.
2. **Pharmacologic antagonism** is the topic of this lesson. It's what happens when we zoom in at the level of an enzyme. And mostly the enzymes we're talking about are cell membrane enzymes called receptors. The receptors are responding to endogenous chemicals and doing their thing. We bring in drugs and mess with those enzymes, alter the function of those receptors. We can manufacture drugs that stimulate or inhibit any receptor. By delivering exogenous compounds, we choose what effect we want, and can do so either directly (drug acts on the receptor) or indirectly (drug acts on something that regulates the activity of the receptor).

Principles of Drugs: Affinity, Efficacy, and Potency

This is the meat of the lesson. And you must have it straight, because the rest of the lesson is manipulation of these concepts. The following terms describe characteristics of the enzyme. They're expressed as dose-response curves: the dose (actually log dose) on the x-axis, and % effect on the y-axis. This becomes important, mapping the axes. Don't attempt to link the common English meaning of a word to its pharmacological function. These words have strict definitions in pharmacology. Learn them.

Affinity is how well a drug binds to a receptor site, to the binding site. Receptor binding is what gets the enzyme to do what it does. It doesn't determine the maximum speed that enzyme can go (that requires saturation of sites, and is efficacy); it determines how fast the enzyme will go with whatever drug is available right now. High affinity means binds really well. **High affinity** means a **smaller dose of drug** is required to have a given effect. Since drug dose is on the x-axis, and **higher affinity** means "**needs smaller dose**," that means high affinity means **smaller x-axis** value—an enzyme with the highest affinity will have a **dose-response curve farthest to the left**. This is the red line marked A.

The **endogenous efficacy** of a system is generally considered to be the $\mathbf{V_{max}}$—the greatest efficacy the system can achieve—and is considered to be 100% efficacious. A drug acting on an enzyme will reach its own V_{max}. The V_{max} is determined by **fully saturating the enzymes**, suppling enough drug so that there is more drug than receptor sites available. **Efficacy is dependent on the number of binding sites available**. It's a property of the number of enzymes there are, irrespective of the current dose. A dose curve will go to its V_{max}. Efficacy is the V_{max} of the dose-response curve, the highest the curve can get. "Highest" means "highest on the y-axis," which means that **the curve with the tallest peak has the greatest efficacy**. This is the green line marked B.

The y-axis is expressed in % Eff, which is the efficacy of the system—the highest known V_{max}. Not all drugs will achieve the 100% efficacy known possible by the system. V_{max} is for the drug. We'll discuss this some more in partial and complete agonists.

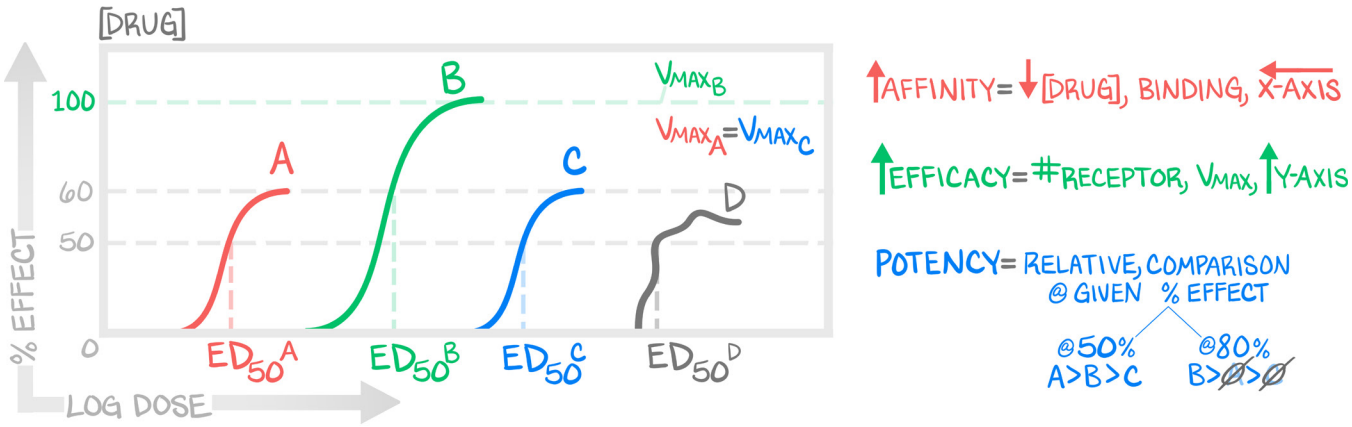

Figure 6.2: Comparing Dose-Response Curves
Red line A and blue line C each have the same height, therefore they have the same maximum possible rate (V_{max}) and therefore we say they have the same efficacy. However, A is farther to the left, meaning it has a higher affinity than C. Green line B has the highest V_{max}, so it has the largest efficacy. Because it's between A and C with regard to the x-axis, it has an affinity in between the two.

Potency is the hardest to handle. It's a **relative** value that compares two drug curves. It's the **affinity** at any given **effectiveness**. To determine this, start at the y-axis. A drug must have a dose-response curve present at the level of efficacy chosen to compare them—that is, the curves have to show up to play the game. The drug with the **highest affinity at the specified efficacy** (leftmost on the x-axis at the specified height on the y-axis) has the greatest potency. Examples will help. In the graph of Figure 6.2, at an Eff of 50% (the blue dashes), the first curve from the left to be encountered is A. That means that at an effectiveness of 50%, A is most potent. However, look at the graph around an effectiveness of 80%. At this effectiveness, A and C have capped out at 60%, and can never reach 80%, so are unable even to be considered. This means that with its effectiveness of 80%, B is most potent.

Principles of Drugs: Shifting the Dose-Response Curve

V_{max} is on the y-axis, and is based on the total number of binding sites. Affinity is the x-axis, and is how well an enzyme binds to its substrate, how much drug is needed to activate the receptor.

	# OF SITES	EFFICACY	Y-AXIS	BINDING	AFFINITY	X-AXIS
Potentiator	No change	No change	No change	↑	↑	Left shift
Competitive Inhibitor	No change	No change	No change	↓	↓	Right shift
Noncompetitive Inhibitor	↓	↓	Down shift	No change	No change	No change

Table 6.1: Anticipating Dose-Response Curve Changes
Change in efficacy/y-axis and affinity/x-axis based on the type of competition.

Competitive Inhibition. If another drug **reversibly binds** to the **binding site**, the two drugs literally compete for that site. The **number of sites doesn't change**. That means the maximum rate, the efficacy, doesn't change (because one could just add more drug and saturate the enzyme with it, outcompeting

the competitor). No change in efficacy means **no change in the y-axis**. But we just said, "you could always add more drug." That effectively means you need a **higher concentration** to elicit the same response. That means the **affinity is lower**, and therefore the **curve shifts to the right**.

Noncompetitive Inhibition. This can happen in one of two ways. The first way is that the drug **irreversibly binds** (covalent bonding) to the binding site. Because the binding is irreversible, that active site is lost for good. The second way is that the drug binds elsewhere other than the active site, but its binding induces a conformation change that **sacrifices the active site**. Either way, the **number of active sites decreases**. Since the maximum efficacy is related to the number of sites, the efficacy must fall, causing a **decrease in the y-axis**. But the remaining binding sites…they're just the same as they always were. They haven't changed their affinity, there are just fewer of them. So, while there's a decrease in the y-axis, there's **no change in the x-axis**.

Potentiation. A potentiator is a drug that binds to the enzyme not at the active site, induces a conformation change that makes the active site better fit its substrate. The number of sites does not change, but the sites that are present are better at binding their substrate. That means there is **no change in the y-axis** (the number of sites remains the same) but because the enzyme is better at binding substrate, it means there is an **increased affinity**, which means the **curve shifts to the left**. The height does not change, but the location on the x-axis is to the left.

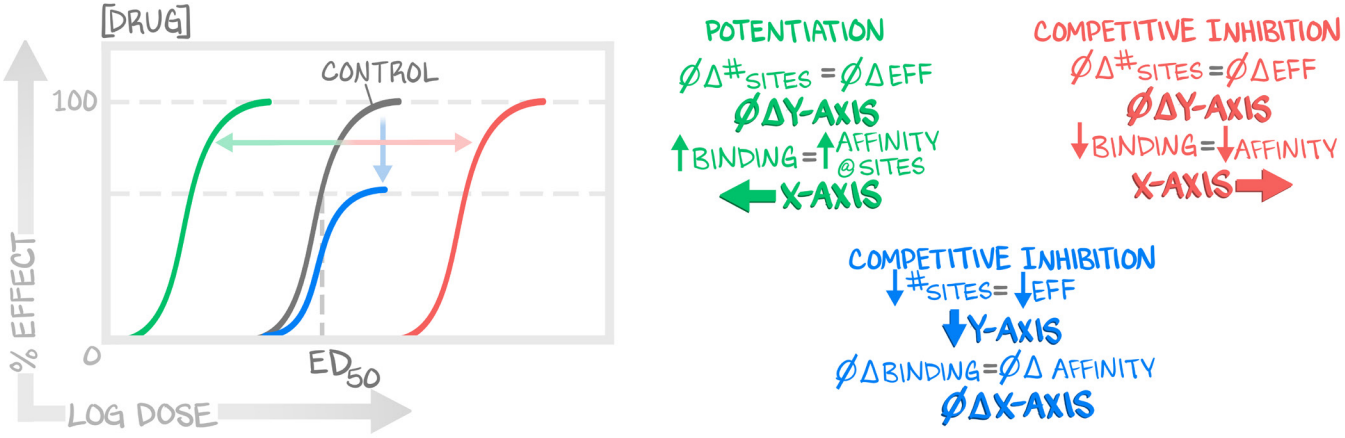

Figure 6.3: Dose-Response Curves
In black is the control, the endogenous relationship of the system if no other drug were added. When a competitive inhibitor is added to the system, the resultant curve is shown in red—the height remains the same but the curve is shifted right. The green line illustrates the effect of adding a potentiator to the system, the opposite of competitive inhibition—the height remains the same but the curve shifts left. The blue line shows the result of adding a noncompetitive inhibitor to the system—binding sites are compromised but the affinity of those remaining is unchanged, resulting only in a drop in the curve's height.

Properties of Drugs: Partial Agonists

From Figure 6.2 we have lines A, B, and C. We already know that **antagonists have an efficacy of 0**, so will have no curve. So why is it, then, that the height of A is different than the height of B? B reaches **100% efficacy** (of the enzyme's known possible rate) **as its own V_{max}**. V_{max} is the "100%" rate of the enzyme charted by green line B. It happens also to be 100% of the system's rate, which is known. There's always 100% effect in any system. The dose-response curve for the drugs you're dealing with may not go to 100% effective for the system. When V_{max} of the dose-response curve is 100% effective for the system, that enzyme is said to be a **complete agonist**. Line B is a **complete agonist**. A and C have their V_{max} at 60%, not 100%. A drug that **fails to achieve 100% regardless of the amount of substrate** is called a **partial agonist**.

We can use partial agonists to our advantage. A **complete agonist** and a **partial agonist** will **compete** for the same receptor site. They are not antagonists; both activate enzyme activity. But **relative** to the complete agonist, the partial agonist limits the number of binding sites, keeping them away from the complete agonist. Thus, as more partial agonists are added into the system with a complete agonist, the partial agonists act as **relative competitive inhibitors** and can limit the efficacy of the complete agonist. Consider, for a moment, a complete agonist that is therapeutic at 60% but toxic at 80% efficacy, but is really easy to take (one pill a day), and reaches 100% with a few doses. This would ensure that the patient would get to toxicity often and rapidly. Add to it a harder-to-take (say, intramuscular once a week) medication that fails to achieve 80% on its own, but in the presence of the first drug, limits that first drug to a new maximum of 75%. Combining these two medications could help with the administration and keep the efficacy from straying beyond therapeutic and into toxicity. More likely, on the exam, you are going to see partial agonism simply as a competitive inhibition, but I did want to relay that it's possible to use this stuff on more than just a dose-response curve.

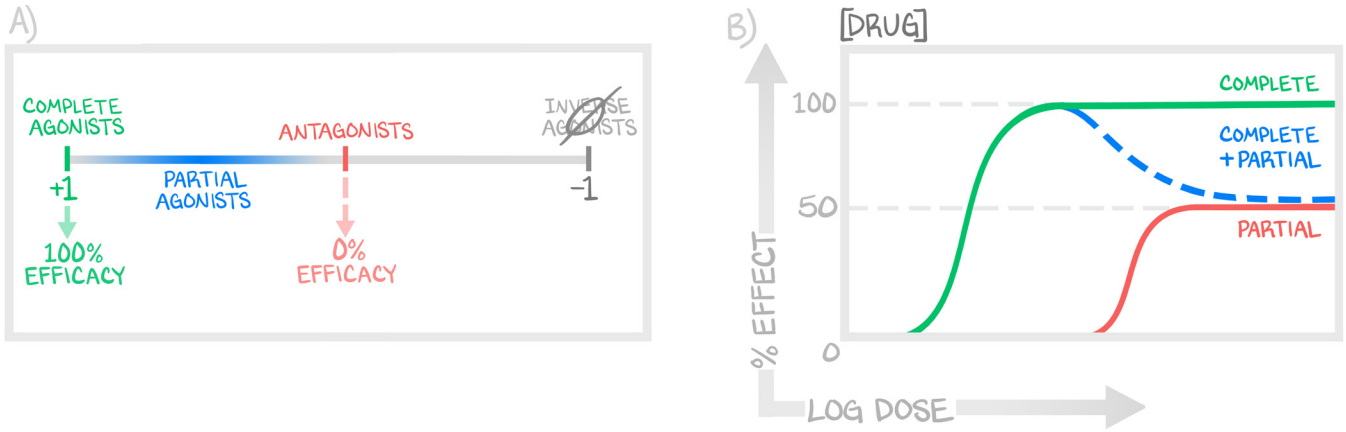

Figure 6.4: Partial Agonists
(a) Complete agonists achieve 100% system efficacy. Antagonists have no efficacy. Inverse agonists you should not learn, and actually have negative function effect. Partial agonists activate a receptor but fail to achieve 100% efficacy. (b) When combined with complete agonists, partial agonists act as an efficacy-limiting drug.

Properties of Populations: Therapeutic Index

HUGE CHANGE IN YOUR MENTAL FOCUS.

Before this moment, I never said the word ED_{50} (effective dose 50). It was in the graph, though. **From this point forward, the same abbreviation "ED_{50}"** means **the dose at which 50% of the population experienced a therapeutic effect**. We're no longer talking about the dose-response curve of a drug to a receptor. We're talking about a dose-response curve of a drug to a population of people in a study.

Just like with comparing drugs, we now compare two curves. The green curve tracks when patients using the medication felt **the intended effect**. At the origin of the curve (nearest the x-y intersection) is the minimum dose for one person to the feel the effect. At the end of the curve (farthest up and right) is the dose at which **everyone will feel the intended effect**. The range between these two is the **therapeutic window**. The ED_{50} is the number we use when comparing safety of a drug because it suggests "middle-of-the-road" or "average."

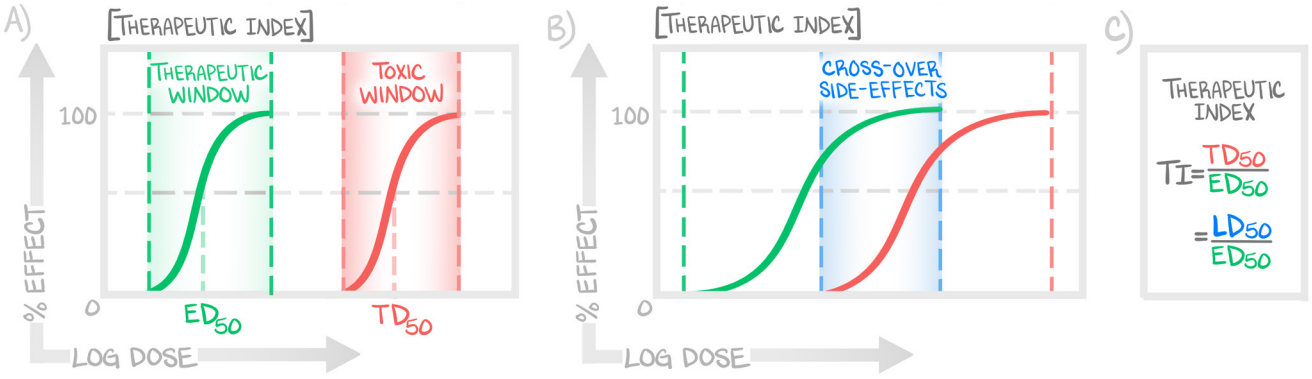

Figure 6.5: Therapeutic Index
(a) Population-response curves demonstrate safety and efficacy. The ED50 is the dose at which 50% of the population achieves therapeutic effect. The TD50 is the dose at which 50% of the population achieves a side effect. While population dose-response curves may look like dose-response curves, they tell a different story. (b) The overlap represents side effects that occur at therapeutic dosing. (c) Therapeutic Index, TI, is calculated as a ration of the toxic dose or the lethal dose to the effective dose.

The red curve shows where patients using the medication experienced a **toxic effect**. That toxic effect is poorly defined in general, and is up to the researcher to define. More particularly, a **lethal dose** (LD) is easier to understand, but toxic dose (TD) is more practical. TD can be described for a particular side effect, any side effect, or the side effect of death. TD for the side effect of death is renamed LD. There's a range for TD and LD just like there is for ED, with the smallest dose where anyone felt any side effect, and a maximum dose that would cause a side effect in everyone who took it. These extreme values are usually tested on animal models first, then human clinical trials bring the dose variation down to actual doseable levels. By beginning extreme with dosing, we gauge how safe a medication is before trying it on humans at regular dosing. Failing to do this could unwittingly expose humans to a potentially lethal dose of a new drug. And because "ED_{50} is a nice average representation," it makes sense to compare ED_{50} to TD_{50} (or LD_{50}).

The therapeutic index (TI) is a marker for the safety of the drug. It's calculated by comparing the **TD_{50}** against the **ED_{50}**. Mathematically, TI is calculated by dividing TD_{50} by ED_{50}. The safest therapeutic index is in the 100s. These are over-the-counter medications. Toxic levels could be reached at 100 times the recommended dose, but that's hard to do accidentally, so anyone can buy them over the counter. Most prescribed medications have therapeutic indices under 100. If an antibiotic has a therapeutic index of 11, and you come home with 14 days' worth of medication to be taken twice a day (28 pills), there's a risk of harm: if the patient takes 11 times the dose at once. Still hard to do accidentally, but easier than ingesting 500 acetaminophens, so requires a prescription. Medications with a therapeutic index in single digits are essentially not given; the risk outweighs the benefit. Medications such as **digoxin** and **chemotherapy** have therapeutic indices in the single digits.

What the therapeutic index doesn't necessarily tell us is the risk of side effects. The **overlap of the dose-response curves** offers insight into the magnitude of side effects. The more overlap, the greater the number of people who will reach a toxic level while still achieving a therapeutic dose. A safe drug is one with no overlap of the two curves, as is shown in the first image on the left. This is why we "try medications" and "assess their response." We have a general idea of the minimum and maximum allowable dose, the side-effect profile, and the safety on a population level, but until we try a medication on the human being in front of us, we won't know how that individual will react.

As an aside, the danger of a drug, the therapeutic index, does NOT set the schedule registered with the DEA. The DEA restricts the prescribing of medications based on their risk of abuse and risk of diversion. Opiates have a high propensity to be abused or diverted, and also happen to have a fairly narrow therapeutic index. They are schedule 2—the most restricted and difficult to prescribe—because people abuse and divert them. Digoxin, by contrast, has a therapeutic index in the single digits, but is not widely abused, and so is not scheduled. Don't confuse ***safety/therapeutic index*** *with the DEA's restriction of medications of abuse.*